PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 45/06, 33/26, 33/30, 31/195

A1

(11) International Publication Number: **WO 98/32464**

(43) International Publication Date: 30 July 1998 (30.07.98)

(21) International Application Number: PCT/GB98/00229

(22) International Filing Date: 27 January 1998 (27.01.98)

(30) Priority Data:
9701675.2 28 January 1997 (28.01.97) GB

(71) Applicant *(for all designated States except US)*: GOLDSHIELD PHARMACEUTICALS LIMITED [GB/GB]; NLA Tower, 12–16 Addiscombe Road, Croydon, Surrey CR9 6BP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BRIDGEMAN, Keith [GB/GB]; 19 Westminster Close, Eastbourne, East Sussex BN22 0LQ (GB).

(74) Agent: McMUNN, Watson, P.; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AT LEAST TYROSINE AND AN IRON COMPOUND FOR TREATING PARKINSON'S DISEASE OR DEPRESSION

(57) Abstract

A pharmaceutical product comprises the use of a combination of tyrosine and iron for separate, sequential or simultaneous administration for the treatment of Parkinson's disease or depression. In a preferred embodiment the product also contains at least one of a vitamin B6 (e.g. pyridoxine), a folate (e.g. folic acid), a vitamin B3 (e.g. nicotinamide), or zinc. The product enables the natural biosynthesis, secretion, transport and action of dopamine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PHARMACEUTICAL COMPOSITION COMPRISING AT LEAST TYROSINE AND AN IRON COMPOUND FOR TREATING PARKINSON'S DISEASE OR DEPRESSION

The invention herein relates to the treatment of Parkinson's disease and/or depression.

Parkinson's disease is a medical disorder whose characteristic symptoms are due to excessive muscle contraction. This often begins as a tremor, which can develop into muscle rigidity, and then to a complete lack of physical movement. Usually, it does not develop until adulthood and becomes progressively more common with age.

It is caused by the insufficient action of dopamine, which normally acts by preventing excessive muscle contraction. Although dopamine is produced in the dopaminergic neurons in the brain, it is not normally administered to treat the disorder since dopamine does not easily pass between the blood brain barrier.

Some existing methods of treating Parkinson's disease make use of dopamine agonists, which mimic the action of dopamine. However, though the use of dopamine agonists can be effective for a while they can cause side effects, and their long term use leads to the progressive desensitisation of the receptors that respond to them.

L-Tyrosine was compared against the use of prominent products for Parkinson's disease and was found to be more effective (Comples Rendus Academie des sciences (III) [1989] 309 (2) : 43-47). The use of iron in the treatment of Parkinson's disease was compared against existing methods of treatment and was found to be beneficial in all patients tested (Journal of Neural Transmission [1986] 67 : 287-292). Zinc deficiency has been shown to lead to, amongst other things, symptoms of Parkinson's disease. It has been reported that nicotinamidadenine dinucleotide (NADH) can be beneficial in the treatment of Parkinson's

disease (Annals of Clinical and Laboratory Science [1989] 19 (1) : 38-43). Tetrahydrobiopterin (BH_4) was also found to have a therapeutic effect on Parkinson's disease patients. (Advances in Neurology 40 : 463-466 and Proceedings Japan Academy series B [1982] 58 : 283-287).

In the early 1940's a number of studies were reported to have been carried out primarily in the USA in which pyridoxine was linked to improvements in Parkinson's disease. (Minnesota Medical Association [1940] 23 : 542, Journal of the American Medical Association [1940] 115 : 839, Minnesota Medicine [1940] 23 : 542, Journal of the American Medical Association [1941] 116 : 1895, and New York State Medical Journal [1941] 41 : 461).

Mental depression (depressive disorders, depressive illnesses) and manic depressive disorders consist of a group of common psychiatric disorders characterised by both mental and somatic symptoms. Treatment includes psychotherapy, electroconvulsive therapy (ECT) and antidepressant drugs such as the manoamine oxidase inhibitors, serotonin reuptake inhibitors and noradrenaline reuptake inhibitors.

It has been reported that a lack of dopamine will cause mental depression. Nicotinamide and similar substances such as nicotinic acid have been used with a fair degree of success in the treatment of depression (Canadian Psychiatric Association [1971] 16 : 413). Pyridoxine has been used in the treatment of depression, and was shown in certain types of cases to be successful (The Lancet [1973] : 897). The deficiency of folic acid folates has been shown to result in depression (Psychological Medicine [1992] 22 : 871).

At present, the most common basis for the treatment of Parkinson's disease is the administration of L-dopa. L-dopa is metabolised to dopamine *in vivo* and, unlike

dopamine, L-dopa can pass the blood brain barrier. However, its administration, via feedback inhibition causes a correspondingly reduced production of the body's own dopamine. Therefore although the use of L-dopa can initially be effective in treating Parkinson's disease, over time it leads to the condition becoming progressively worse. There are also side effects caused by the use of L-dopa.

It is an object of the invention(s) to provide an effective treatment for Parkinson's disease and depression, and particularly more effective than L-dopa.

It is a further object to obviate or mitigate the disadvantages of treatment with L-dopa.

According to the first aspect of the present invention there is provided the use of a combination pharmaceutical product of at least tyrosine or a pharmacologically acceptable derivative thereof and an iron containing compound in the preparation of medicament for the treatment or prophylaxis of Parkinson's disease and depression. The combination can be given separately, sequentially, simultaneously or as a combined unitary drug product. Thus for example, a blister pack containing iron and tyrosine as separate tablets to be given together would be within the scope of the invention. However a unitary tablet or capsule containing the combination is preferred.

A second aspect of the invention provides a pharmaceutical product comprising tyrosine or a pharmacologically acceptable derivative thereof together with an iron containing compound for combined separate, sequential or simultaneous administration for the treatment or prophylaxis of Parkinson's disease or depression.

Unlike L-dopa, the invention can be used long term without significant side effects since it enables the

natural biosynthesis, secretion, transport and action of the body's own dopamine.

By pharmacologically acceptable derivative of tyrosine, we mean to include any precursor which will metabolise to tyrosine *in vivo* such as phenylalanine (typically the L-phenylalanine). Ideally, L-tyrosine or DL-tyrosine and salts is administered in accordance with the invention. A suitable daily dosage of tyrosine (typically L-tyrosine) or derivative in accordance with the invention is 240mg to 6000mg, preferably 1200mg to 3600mg, typically about 2400mg.

Iron should also be available *in vivo* with tyrosine and so any compounds or element which delivers iron *in vivo* is an iron containing compound in accordance with the invention. Preferably the iron containing compound contains ferrous iron (e.g. ferrous sulphate or a ferri-ferro complex e.g. oxyferriscarbone™) since this appears to be absorbed better by the body. Ferrous iron is used in the biosynthesis of dopamine. Suitable total daily dosage of iron in an iron containing compound is 2mg to 100mg, preferably 10mg to 30mg, typically about 20mg iron. If the iron is present as iron sulphate then the weight of iron containing compound would be higher such as 54mg ferrous sulphate (corresponding with 20mg Fe^{3+}).

Preferably the combination product of the invention also comprises for separate, sequential, simultaneous administration or administration as a combined preparation, at least one of a vitamin B6 (e.g. pyridoxine), a folate (e.g. folic acid), a vitamin B3 (e.g. nicotinamide) or a zinc containing compound.

Advantageously, the combination of the invention comprises at least one vitamin B6 such as pyridoxal and pyridoxamine. However, most preferably the vitamin B6 is substantially pryridoxine or a pharmacologically acceptable

salt thereof such as pyridoxine hydrochloride. Suitably the total daily dose of vitamin B6 (such as pyridoxine) is 0.2mg to 240mg, more preferably 1.2mg to 3.6mg, typically about 2.4mg.

It is further preferred that a folate is administered in the combination of the invention. Most preferably folic acid is used. A suitable total daily dose of folate (such as folic acid) is 0.04mg to 10mg, preferably 0.2mg to 0.8mg, typically 0.4mg.

Further preferably at least one vitamin B3 such as nicotinic acid is present in the combination of the invention, but ideally nicotinamide is present. A suitable total daily dose of vitamin B3 (such as nicotinamide) is 2mg to 500mg, preferably 10mg to 30mg, typically 20mg.

Yet further preferably, a zinc containing compound such as zinc sulphate is also present in the combination of the invention, so as to deliver Zn^{2+} *in vivo*. A suitable daily dose of a zinc containing compound is 2mg to 80mg, preferably 10mg to 30mg, typically 20mg (which corresponds to 50mg zinc sulphate).

Where a derivative of a compound of the combination is mentioned, we mean to include salts, esters, amides and other precursors which will metabolise to the compound of interest *in vivo*.

Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, for example, salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic,

oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, benzenesulphonic, and isethionic acids.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or ships; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

The unit dosage form of the invention can be given one, two, three, four or more times a day in accordance with the total daily dosages recommended hereinbefore. Thus for a four times daily treatment, a unit dosage would

suitably contain 60mg to 1500mg tyrosine or derivative (i.e. 240mg to 6000mg divided by 4) and 0.5mg to 25mg of iron present as an iron containing compound. Preferably it would also contain 0.5mg to 20mg vitamin B6 and/or 0.01mg to 2.5mg folate and/or 0.5mg to 125mg vitamin B3 and/or 0.5mg to 20mg of zinc present as a zinc containing compound. Similarly if a three times daily dose was administered, then the unit dosage form would be a multiple of three of the total daily dosage.

Further aspects of the invention are as follows:

a) a method for the treatment of Parkinson's disease or depression which comprises administering in therapeutic amounts to the patient separately, sequentially or as a combined product, the combination of tyrosine or a pharmacologically acceptable derivative thereof and an iron containing compound;

b) an anti-depressant or anti-Parkinson's disease pharmaceutical composition (such as a tablet, powder or capsule) comprising tyrosine or a pharmacologically acceptable derivative thereof, an iron containing compound and a pharmaceutically acceptable carrier;

As a broader principle to the combinations outlined hereinbefore, it is proposed that tyrosine alone, zinc alone, and iron alone will be useful in the treatment of depression (although a combination is preferred).

Accordingly, there is further provided:

c) use of a compound selected from the group consisting of tyrosine or a pharmacologically acceptable derivative thereof, an iron containing compound, and a zinc containing compound in the preparation of a medicament for the treatment or prophylaxis of

depression (the total daily dosages dosage forms and the preferred actives are as given hereinbefore); and

d) a method for the treatment or prophylaxis of depression comprising administering to the patient, therapeutic amounts of a compound selected from the group consisting of tyrosine or a pharmacologically acceptable derivative thereof, an iron containing compound and a zinc containing compound.

For the treatment of depression, preferably there is also a component present which produces a sustained high level of blood sugar.

An example of a tablet or capsule in accordance with the invention for the treatment of Parkinson's disease and depression has the following active ingredients:

600.00mg	L-Tyrosine
13.50mg	Ferrous sulphate (dried)
12.50mg	Zinc sulphate (dried)
5.00mg	Nicotinamide
0.60mg	Pyridoxine hydrochloride
0.10mg	Folic acid

A total of four tablets may be taken every day by the patient for several months until a beneficial improvement is obtained. The dosages are based on average 70kg adult, and so a heavier adult may benefit from higher daily dosages. Similarly Parkinson's disease patients who have previously been treated with L-dopa may benefit from higher dosages.

CLAIMS

1. A pharmaceutical product comprising tyrosine or a pharmacologically acceptable derivative thereof together with an iron containing compound for combined separate, sequential or simultaneous administration for the treatment or prophylaxis of Parkinson's disease or depression.

2. A pharmaceutical product as claimed in Claim 1 wherein the tyrosine or derivative is L-tyrosine.

3. A pharmaceutical product as claimed in Claims 1 or 2 wherein the dosage of tyrosine or derivative is 60mg to 1500mg.

4. A pharmaceutical product as claimed in any one of the preceding claims wherein the iron in the iron containing compound is present as ferrous iron.

5. A pharmaceutical product as claimed in any one of the preceding claims wherein the dosage of iron in the iron containing compound is 0.5mg to 25mg.

6. A pharmaceutical product as claimed in any one of the preceding claims which further comprises a vitamin B6.

7. A pharmaceutical product as claimed in Claim 6 wherein the vitamin B6 is pyridoxine or a pharmacologically acceptable salt thereof.

8. A pharmaceutical product as claimed in Claim 6 or 7 wherein the dosage of vitamin B6 is 0.05mg to 60mg.

9. A pharmaceutical product as claimed in any one of the preceding claims which further comprises a folate.

10. A pharmaceutical product as claimed in Claim 9 wherein the folate is folic acid.

11. A pharmaceutical product as claimed in Claim 9 or 10 wherein the dosage of folate is 0.01mg to 2.5mg.

12. A pharmaceutical product as claimed in any one of the preceding claims which further comprises a vitamin B3.

13. A pharmaceutical product as claimed in Claim 12 wherein the vitamin B3 is nicotinamide.

14. A pharmaceutical product as claimed in Claim 12 or 13 wherein the dosage of vitamin B3 is 0.5mg to 125mg.

15. A pharmaceutical product as claimed in any one of the preceding claims which further comprises a zinc containing compound.

16. A pharmaceutical product as claimed in Claim 15 wherein the dosage of zinc in the zinc containing compound is 0.5mg to 20mg.

17. A pharmaceutical product comprising as a unitary dosage form tyrosine or a pharmacologically acceptable derivative thereof, an iron containing compound, a vitamin B6, a folate, a vitamin B3, and a zinc containing compound.

18. A pharmaceutical product as claimed in any one of the preceding claims in the form of a unitary tablet, capsule or powder containing the active compounds.

19. Use of a pharmaceutical product as claimed in any one of the preceding claims for the treatment or prophylaxis of Parkinson's disease or depression.

20. Use of a compound selected from the group consisting of tyrosine or a pharmacologically acceptable derivative thereof, an iron containing compound, and a zinc containing

compound in the preparation of a medicament for the treatment or prophylaxis of depression.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/GB 98/00229

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K33/26 A61K33/30 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 292 522 A (G.C. CONWAY) 28 February 1996 see page 1, line 1-3, paragraph 4 see page 2, line 5 - page 4, line 2 see page 7, line 24-25; examples 3,5 see claims 1-14,23 ---	1-20
X	GB 2 268 871 A (BIO NUTRITIONAL HEALTH SERVICE) 26 January 1994 see page 4, line 25 - page 5, line 9; claims 1,10-13,15-17; examples 15,19,23 see page 9, line 25 - page 10, line 11 see page 13, line 21-25 see page 16, line 25 see page 18, line 17-28 --- -/--	1,2,4-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 1998	27.05.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 98/00229

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9608 Derwent Publications Ltd., London, GB; AN 96-074740 XP002064384 & JP 07 330 583 (TERUMO CORP) , 19 December 1995 see abstract & JP 07 330 583 A (TERUMO CORP) ---	1-11,15, 16
X	DE 41 37 944 A (IND TECHNOLOGY RESEARCH INDSTI) 21 May 1992 see page 2, line 7; claims 1,3-5 see page 4, line 28-30 see page 5, line 9-14; example 1; table 1 see page 3, line 38-40 ---	1,2,4, 19,20
X	DATABASE WPI Week 8344 Derwent Publications Ltd., London, GB; AN 83-805362 XP002064385 & JP 58 162 515 (TANABE SEIYAKU CO) , 27 September 1983 see abstract & JP 58 162 515 A (TANABE SEIYAKU CO) ---	1-5,15, 16
X	DATABASE WPI Week 8834 Derwent Publications Ltd., London, GB; AN 88-240841 XP002064386 & RO 94 381 (INTR MEDICAMENTE TERAPIA) , 30 April 1988 see abstract & RO 94 381 A (INTR MEDICAMENTE TERAPIA) ---	1,4,6,7, 9,10
X	US 4 167 564 A (JENSEN NED L) 11 September 1979 see claims 1,2,9-11; examples 3,6 -----	1,2,4

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/GB 98/00229

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 19 is directed to a method of treatment of the human/animal body, the searcj has been carried out and based on the alleged effects od the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/GB 98/00229

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2292522 A	28-02-96	NONE	
GB 2268871 A	26-01-94	AU 4509993 A	31-01-94
		WO 9401006 A	20-01-94
DE 4137944 A	21-05-92	US 5122461 A	16-06-92
		JP 4311394 A	04-11-92
US 4167564 A	11-09-79	NONE	